6 and 12 nucleotides or nucleotide pairs.

3. (Amended) A crystallized complex for use in X-ray crystallography comprising:

a. an HCV NS3 helicase protein selected from SEQ ID NO:2; fragments of SEQ ID NO:2 comprising at least amino acids 183 to 582; mutants of SEQ ID NO:2 containing one or more of the following amino acid substitutions: Ser231-to-Ala, Thr269-to-Ala, Ser370-to-Ala, Thr411-to-Ala, Trp501-to-Phe, Trp501-to-Leu or Trp501-to-Ala, Gln460-to-Ala, Arg461-to-Ala, Arg462-to-Ala, Arg464-to-Ala, or Arg467-to-Ala; or fragments of SEQ ID NO:2 comprising at least amino acids 183 to 582 and containing one or more of the following amino acid substitutions: Ser231-to-Ala, Thr269-to-Ala, Ser370-to-Ala, Thr411-to-Ala, Trp501-to-Phe, Trp501-to-Leu or Trp501-to-Ala, Gln460-to-Ala, Arg461-to-Ala, Arg462-to-Ala, Arg464-to-Ala, or Arg467-to-Ala; and

b. a single-stranded oligonucleotide consisting of between 6 and 12 nucleotides or nucleotide pairs.

B1 Cont'd

REMARKS

Applicants have cancelled claims 5 and 6 without prejudice to their right to file for and obtain claims directed to the canceled subject matter in applications claiming priority from the present application under 35 U.S.C. §120.

Applicants have amended claims 1-3 in response to the Examiner's

rejections and in order to make the claims more commensurate in scope with the invention. In particular, applicants have amended claims 1 and 3 to recite the specific NS3 helicase proteins disclosed in the application -- SEQ ID NO:2; fragments of SEQ ID NO:2 comprising at least amino acids 183 to 582; mutants of SEQ ID NO:2 containing one or more of the following amino acid substitutions: Ser231-to-Ala, Thr269-to-Ala, Ser370-to-Ala, Thr411-to-Ala, Trp501-to-Phe, Trp501-to-Leu or Trp501-to-Ala, Gln460-to-Ala, Arg461-to-Ala, Arg462-to-Ala, Arg464-to-Ala, or Arg467-to-Ala; or fragments of SEQ ID NO:2 comprising at least amino acids 183 to 582 and containing one or more of the following amino acid substitutions: Ser231-to-Ala, Thr269-to-Ala, Ser370-to-Ala, Thr411-to-Ala, Trp501-to-Phe, Trp501-to-Leu or Trp501-to-Ala, Gln460-to-Ala, Arg461-to-Ala, Arg462-to-Ala, Arg464-to-Ala, or Arg467-to-Ala. Support for this amendment is found in the specification at page 12, line 19 to page 13, line 17.

In addition, claim 1 has been amended to better define the oligonucleotide as one consisting of between 6 and 12 nucleotides or nucleotide pairs and claim 3 has been amended to define the oligonucleotide as being single stranded and consisting of between 6 and 12 nucleotides. As set forth in the specification, if a double stranded oligonucleotide is used in a crystallizable composition, it is denatured prior to crystallization (see page 14, lines 5-8). Thus, the oligonucleotide portion of the crystallized complexes of this invention is always single stranded

Claim 2 has been amended to refer to SEQ ID NO:2, rather than SEQ ID NO:1. SEQ ID NO:2 represents the amino acid sequence encoded by SEQ ID

NO:1 and although the translated amino acids are listed in SEQ ID NO:1, that sequence is properly a nucleotide sequence and thus should not be referenced for the encoded amino acids.

None of these amendments add new matter.

Applicants confirm that their election of claims 1-6 in their September 21, 2000 Reply to Office Action was made without traverse.

Claims 1-6 stand rejected under 35 U.S.C. §112, first paragraph as not being enabled. The Examiner contends that the specification "does not reasonably provide enablement for all crystalline compositions and methods ... encompassed by the claims." In support of her position, the Examiner cites D. G. Brown et al., "Crystallography in the Study of Protein-DNA Interactions" In Methods in Molecular Biology Vol. 56: Crystallographic Methods and Protocols, C. Jones et al., eds., Humana Press Inc, Totowa, NJ, pp. 293-318 (1996) ("Brown et al.") as suggesting that crystallization of protein-DNA complexes is not predictable and requires extensive experimentation to develop crystals suitable for X-ray crystallography. As further support, the Examiner cites the "substantially different" conditions used by N. Yao et al., Nat. Struct. Bio., 4, pp. 463-67 (1997) ("Yao et al.") to crystallize NS3 helicase without being complexed to an oligonucleotide.

The Examiner further contends that the specification defines "HCV NS3 helicase protein" as including proteins containing non-helicase related amino acid sequences on both the N- and C-terminal ends, as well as mutations containing deletions, substitutions and insertions and thus does not clearly define the metes and

bounds of that term. Applicants traverse based upon the claim amendments presented herein.

The amended crystallizable composition and crystallized complex claims presented herein specifically define the HCV NS3 helicase protein as having an amino acid sequence of SEQ ID NO:2, a fragment of SEQ ID NO:2 comprising at least amino acids being identical to 183-582, or specific amino acid substitution mutants of the above. In addition, the oligonucleotide in these compositions, complexes and methods is also specifically defined as consisting of 6 to 12 bases or base pairs. Thus, the amended claims encompass a small, well-defined group of HCV NS3 helicase proteins and oligonucleotides which are very closely related to and supported by the exemplified crystals in the application.

There is nothing in Brown et al. that suggests that applicants' disclosed crystallization methods will not be effective in producing X-ray crystallographic quality crystals for each and every complex encompassed by the amended claims. Applicants believe that Brown et al. stands for the proposition that identifying crystallization conditions for a previously uncrystallized protein-DNA complex requires experimentation. That reference does not, however, suggest that a known crystallization methodology for a given protein-DNA complex would not be effective in crystallizing highly related complexes, such as those encompassed by the amended claims presented herein. For example, Brown et al. state:

"Thus there remain a large number of DNA binding proteins where no structural information is yet available and about which little structural interpretation is known.

The starting point for any X-ray crystallographic investigation of protein-DNA interaction is the growth of suitable protein-DNA co-crystals." (p. 297, 2nd to 3rd paragraph)

Applicants have gone well past this initial step by presenting information about and protocols for crystallizing a HCV NS3 helicase protein-oligonucleotide complex that is closely related to all HCV NS3 helicase protein-oligonucleotide complexes encompassed by the amended claims.

Furthermore, applicants fail to see the relevance of the Examiner's citation to Yao et al. Applicants admit freely that the protocol used by Yao et al. differs from their invention. But Yao et al. was not concerned with crystallizing a NS3 helicase protein-oligonucleotide complex. The lack of an oligonucleotide in the Yao et al. crystals make those crystals very different from those claimed by the present applicants. The relationship between the Yao et al. crystals and any of applicants' claimed crystals is far more distant than that between each of applicants' claimed crystals. Thus, the Examiner's premise that the Yao et al. "complex" (although not a complex at all) and applicants' complex are "similar" in incorrect. Moreover, the Examiner has provided no proof that applicants' protocol could not be used to crystallize a NS3 helicase protein in the absence of an oligonucleotide. Therefore, the fact that Yao et al. used a different protocol for a very different crystal is of no import. Accordingly, amended claims 1-4 do satisfy 35 U.S.C. §112, first paragraph.

The Examiner advises applicants that the terms "crystallizable complex" and "crystallized complex" in the claims are interpreted as being suitable for producing X-ray crystallographic quality crystals. Applicants confirms this interpretation, and for clarity have amended the claims to refer to "crystallizable composition capable of producing crystals for use in X-ray crystallography", "crystallized complex for use in X-ray crystallography", and "[a] method of producing a crystallized complex comprising an HCV NS3 helicase and an oligonucleotide for use in X-ray crystallography."

Claims 1-2 and 5-6 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite. In particular, the Examiner notes that claims 2 and 6 refer to an amino acid range in SEQ ID NO:1, which is a DNA sequence. Applicants have obviated this rejection by amending claim 2 to refer to SEQ ID NO:2, the amino acid sequence encoded by SEQ ID NO:1, and canceling claims 5-6.

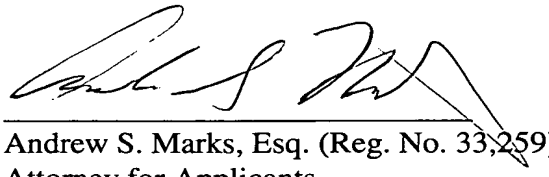
The Examiner also states that claim 5, step (a) refers to crystallizable compositions, but wonders how one could obtain a crystallizable composition without already having determined that it can be crystallized. In step (b) of claim 5, the Examiner states that subjecting the composition to conditions which promote crystallization generically may or may not result in a crystallized compositions. Applicants have obviated this rejection by canceling claim 5.

Claim 1 stands rejected under 35 U.S.C. §102(b) as being anticipated by K. Morgenstern et al., J. Virol., 71, pp. 3767-75 (1997) ("Morgenstern et al."). Specifically, the Examiner asserts that Moregnestern et al. discloses a composition which

contains an HCV NS3 helicase and an oligonucleotide which, if frozen, would produce crystals. Applicants have obviated this rejection by amending claim 1 to recite "[a] crystallizable composition capable of producing crystals for use in X-ray crystallography." This amendment overcome the §102 rejection as Morgenstern et al. does not teach or suggest producing X-ray crystallographic quality crystals of a HCV NS3 helicase-oligonucleotide complex.

Applicants request that the Examiner enter the claim amendments presented herein, consider the forgoing remarks and allow this application to pass to issue.

Respectfully submitted,



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APPENDIX 1

1. (Amended) A crystallizable composition capable of producing crystals for use in X-ray crystallography comprising:

a. an HCV NS3 helicase protein selected from SEQ ID NO:2; fragments of SEQ ID NO:2 comprising at least amino acids 183 to 582; mutants of SEQ ID NO:2 containing one or more of the following amino acid substitutions: Ser231-to-Ala, Thr269-to-Ala, Ser370-to-Ala, Thr411-to-Ala, Trp501-to-Phe, Trp501-to-Leu or Trp501-to-Ala, Gln460-to-Ala, Arg461-to-Ala, Arg462-to-Ala, Arg464-to-Ala, or Arg467-to-Ala; or fragments of SEQ ID NO:2 comprising at least amino acids 183 to 582 and containing one or more of the following amino acid substitutions: Ser231-to-Ala, Thr269-to-Ala, Ser370-to-Ala, Thr411-to-Ala, Trp501-to-Phe, Trp501-to-Leu or Trp501-to-Ala, Gln460-to-Ala, Arg461-to-Ala, Arg462-to-Ala, Arg464-to-Ala, or Arg467-to-Ala; and

b. an oligonucleotide consisting of between 6 and 12 nucleotides or nucleotide pairs.

2. (Amended) The composition according to claim 1, wherein said HCV NS3 helicase comprises amino acids 167-631 of [SEQ ID NO:1] SEQ ID NO: 2 and wherein said oligonucleotide is a single stranded polynucleotide consisting of between 6 and 12 nucleotides or nucleotide pairs [in length].

3. (Amended) A crystallized complex for use in X-ray crystallography comprising:

a. an HCV NS3 helicase protein selected from SEQ ID NO:2; fragments of SEQ ID NO:2 comprising at least amino acids 183 to 582; mutants of SEQ ID NO:2 containing one or more of the following amino acid substitutions: Ser231-to-Ala, Thr269-to-Ala, Ser370-to-Ala, Thr411-to-Ala, Trp501-to-Phe, Trp501-to-Leu or Trp501-to-Ala, Gln460-to-Ala, Arg461-to-Ala, Arg462-to-Ala, Arg464-to-Ala, or Arg467-to-Ala; or fragments of SEQ ID NO:2 comprising at least amino acids 183 to 582 and containing one or more of the following amino acid substitutions: Ser231-to-Ala, Thr269-to-Ala, Ser370-to-Ala, Thr411-to-Ala, Trp501-to-Phe, Trp501-to-Leu or Trp501-to-Ala, Gln460-to-Ala, Arg461-to-Ala, Arg462-to-Ala, Arg464-to-Ala, or Arg467-to-Ala; and

b. [an] a single-stranded oligonucleotide consisting of between 6 and 12 nucleotides or nucleotide pairs.